Exploration of the Synthesis and Reactivity of 2-*tert*-Butoxy-1-methylpyridinium Triflate

An Honors Thesis (HONRS 499)

by

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Abstract

2-Benzyloxy-1-methylpyridinium triflate has been shown to be an effective reagent for benzylating oxygen nucleophiles under neutral conditions and mild temperatures. It has been proposed that upon heating, the title reagent decomposes to a benzyl cation followed by trapping of the reactive intermediate with an oxygen nucleophile. Specifically, it has been used to successfully benzylate alcohols, carboxylic acids, and phenols. The focus of this project is to extend the utility of oxypyridinium salts to include transfer of *tert*-butyl groups to oxygen nucleophiles. Initial studies focused on the synthesis and reactivity of 2-*tert*-butoxy-1-methylpyridinium triflate. Second, the reaction conditions required for the *in situ* generation of the key reagent and subsequent generation of *tert*-butyl ethers were explored.

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I would like to thank Gus Olynger and Megan Noonan for keeping me company in the lab this past summer and thank you to my fiancée, Erika Vitols, for putting up with me when I became frustrated with my research. Lastly, I would like to thank my parents. Without them I would not be where I am today.

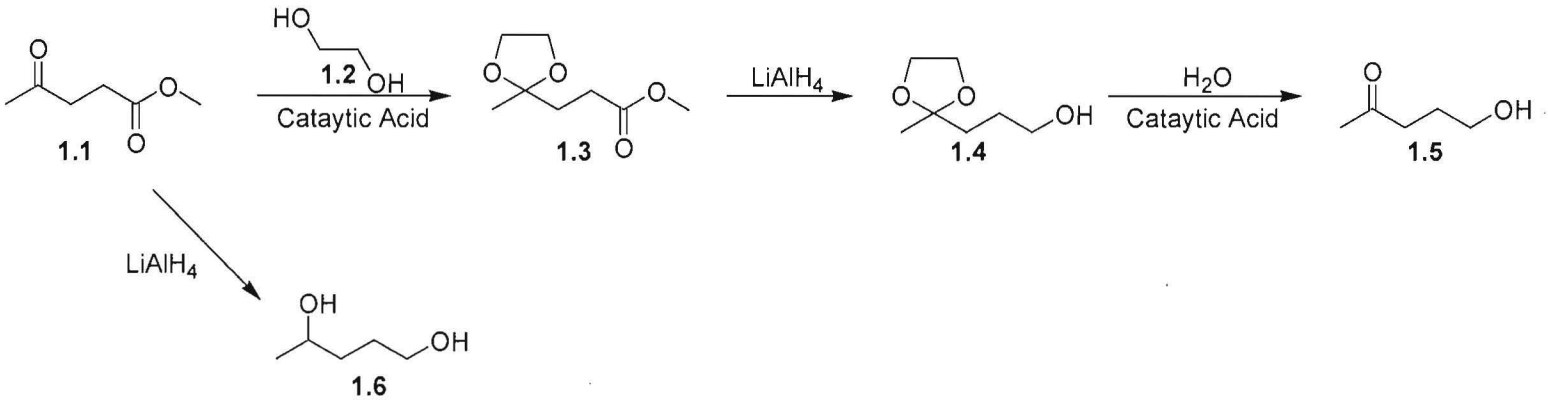
Author's Statement

The purpose of this research is to find a new, easier way to make an organic bond. Since almost everything is composed of such bonds, these reactions are very important and very useful. They can be used in creating new pharmaceuticals, biological molecules such as carbohydrates and amino acids, pesticides, polymers and many other items germane to our everyday lives. Having new ways of making these bonds can lead to compounds like pharmaceuticals being made cheaper and more efficiently. It can also lead to new molecules that could not previously be made such as a certain anti-cancer drug.

This research was presented at a Ball State University Chemistry Department Organic Super Group meeting. It was also presented at the 12th Annual Indiana local section American Chemical Society's Region 11 Poster Session in Indianapolis, IN on October 13, 2011.

Background and Significance

When synthesizing complex multifunctional compounds such as nucleotides, polypeptides, carbohydrates, and many pharmaceuticals, a reaction sometimes needs to be carried out on one reactive center without affecting other reactive sites. Often a particular chemical environment can cause unwanted side reactions on other functional groups in a molecule such as reductions or oxidations. This is when a protecting group is needed. A protecting group temporarily blocks other reactive centers in a molecule by rendering them inert to the reaction taking place on the desired functionality. This protecting group can then be cleaved to yield the original functional group. An example of the utility of a protecting group is shown in Scheme 1.1.



Scheme 1.1 An Example of the Utility of a Protecting Group

As Scheme 1.1 shows, **1.1** has two functionalities, a ketone and ester, which can both be reduced to an alcohol. If one aimed to only reduce the ester using $LiAlH_4$, a common reducing agent, without reducing the ketone, the ketone can first be protected as an acetal to yield **1.3**. $LiAlH_4$ can then be introduced to yield **1.4** followed by the cleavage of the protecting group to

give the original ketone and the reduced ester in **1.5**. Conversely, if $LiAlH_4$ were reacted with **1.1**, both of the functionalities would be reduced to an alcohol to give molecule **1.6**.

Scheme 1.1 also shows the three major steps required when utilizing a protecting group. First, the protecting group is installed. Next, the desired reaction is carried out without interference from the protecting group. Finally, the protecting group is cleaved to give the molecule its original functionality. In this process, the protecting and deprotecting do not further the overall synthesis. This leads to some criteria that a protecting group must posses. In order to be successful a protecting group must:[1]

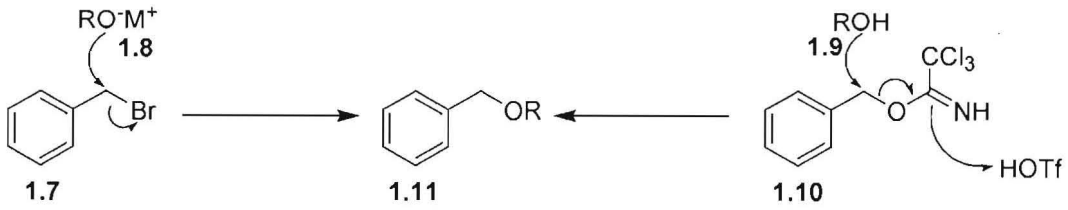
- React selectively in high yields to protect the target functional group
- Be stable to the projected reaction conditions
- Be selectively removed in high yields, preferably by nontoxic reagents
- Be stable to purification methods
- Not generate new stereogenic centers
- Have minimum functionality so as not to introduce further reaction sites

Also, it can be advantageous to protect multiple functionalities within the same molecule with the same protecting group. This way the groups can be installed and removed simultaneously.[1]

A common functionality that often needs to be protected during synthesis is the hydroxyl group. There are many different protecting groups that can be used to mask a hydroxyl group. Of particular interest in our lab has been the benzyl group. This is one of the most common protecting groups and like other alkyl protecting groups it is stable to a wide range of reaction conditions.[1] Additionally, it is cleaved in a variety of ways making it very useful. One of the most common ways to cleave a benzyl group is through hydrogenolysis using H_2/Pd-C.[2] Single electron reduction can also be achieved by using mixing the ether with $Na/NH_{3(l)}$ for only 15

seconds.[3] Lewis-acid based methods can be used as well. One such strategy uses 1.3 equivalents of Me_3SiI in CH_2Cl_2 at 25 °C for 15 minutes to give a 100% yield of the deprotected alcohol.[4] Lastly, the benzyl group can be oxidized to a benzoate and then hydrolyzed under basic conditions. One example uses CrO_3 in acetic acid at 25 °C to give a benzoate which can then be cleaved to the corresponding alcohol.[5]

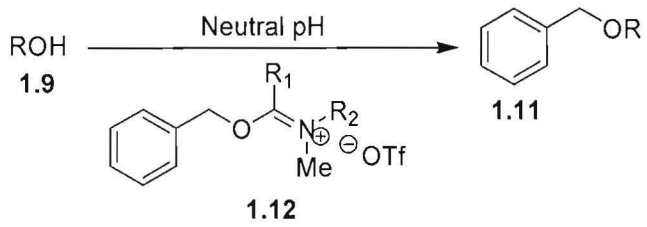
The two main methods of installing a benzyl group on an alcohol are either the Williamson ether synthesis[6] or using a protonated trichloroacetimidate,[7] as shown in Scheme 1.2. The first step of the Williamson ether synthesis requires a strong base to yield **1.8** from **1.9**. An S_N2 reaction can then occur between **1.8** and **1.7** to give benzyl ether **1.11**. Alternatively, the trichloroacetimidate **1.10** can be used. This must first be activated by protonation with triflic acid (HOTf), a very strong acid. This gives the nitrogen a positive formal charge making the reaction more favorable. The drive behind this route to making **1.11** is the electrons being shuffled around to eventually cancel out the newly generated positive charge on the nitrogen. These reactions require extreme basic or acidic conditions. Since most functionalities can not withstand these harsh conditions, a neutral method must be used when dealing with complex molecules.



Scheme 1.2 Williamson Ether Synthesis (left) and a Protonated Trichloroacetimidate (right)

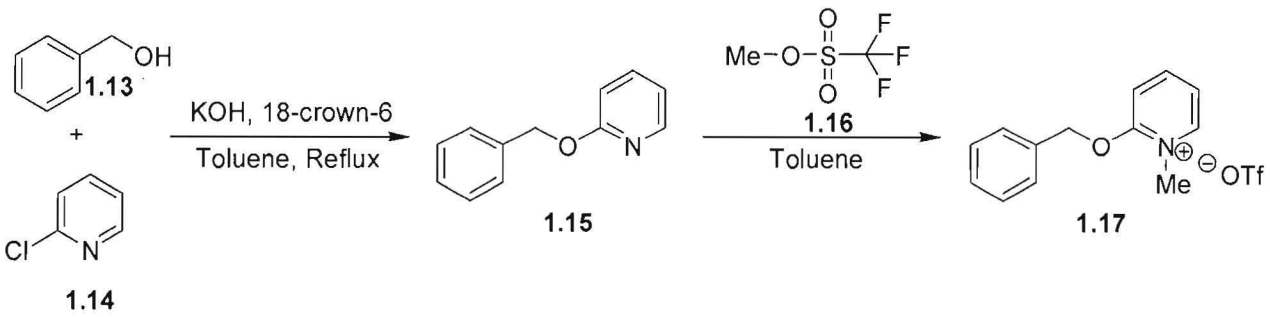
A preactivated version of **1.10**, shown in Scheme 1.3, was the initial motivation behind the synthesis of 2-benzyloxy-1-methylpyridinium triflate or Bn-OPT (**1.17**).[8] It was postulated

that if a molecule like this could be synthesized then this benzyl transfer could be carried out under relatively neutral conditions.



Scheme 1.3 A Preactivated Trichloroacetimidate under Neutral Conditions

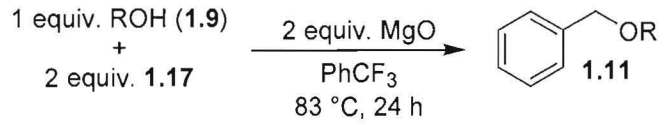
1.12 is preactivated by the presence of the methyl group and triflate counter ion. This gives the nitrogen a positive formal charge leading to the same type of reaction seen in Scheme 1.2 but without the need for triflic acid. Bn-OPT was made to fit the model of **1.12** because pyridinium salts like Mukaiyama's reagent had previously shown utility in esterification reactions.[9] The synthesis of Bn-OPT[10] shown in Scheme 1.4 is straight forward starting with the oxygen of **1.13** replacing the chlorine of **1.14** via nucleophilic aromatic substitution. The nitrogen on **1.15** is then methylated by methyl triflate or MeOTf (**1.16**) to give Bn-OPT (**1.17**).



Scheme 1.4 Two-Step Synthesis of Bn-OPT[10]

Bn-OPT has been shown to be an effective benzylating agent for 1°, 2° and 3° alcohols under relatively neutral conditions. It is a bench stable salt and its utility has been expanded to include benzyl transfer to carboxylic acids[11] and electron rich aromatics.[12] Research benzylating

amines is currently being pursued as well. Yields for 1° and 2° alcohols are usually very high with typical yields around 90% (Table 1.1).[13]



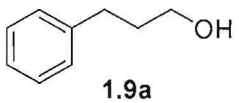
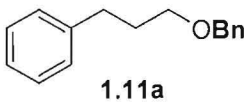
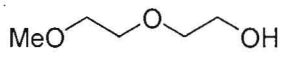
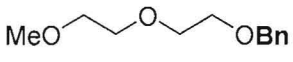
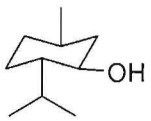
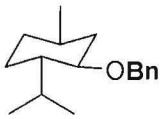
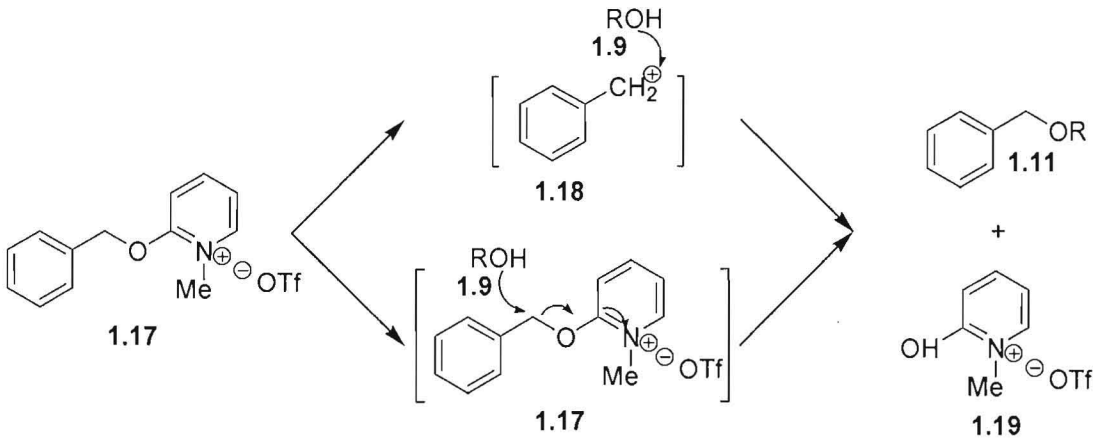
Alcohol (1.9)	Benzyl Ether (1.11)	Yield (%)
 1.9a	 1.11a	>95
 1.9b	 1.11b	93
 1.9c	 1.11c	88

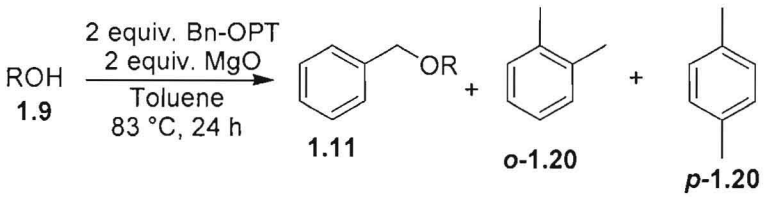
Table 1.1 Reported Yields Reacting ROH with Bn-OPT[13]

The mechanism for the benzylation of alcohols via Bn-OPT can potentially follow one of two extreme pathways, either an S_N2 or an S_N1 pathway (Scheme 1.5). If this reaction proceeds by an S_N2 mechanism then **1.9** first attacks the backside of the benzylic carbon of **1.17** breaking the bond to the adjacent oxygen. The electrons of the stable leaving group can then be shuffled around to cancel out the positive formal charge on the nitrogen. Eventually the formal charge is regenerated as the oxygen of **1.19** picks up the extra hydrogen from the substitution reaction between **1.9** and **1.17**. If this reaction proceeds via an S_N1 route, Bn-OPT first decomposes during heating to yield the benzyl carbocation **1.18**. The lone pair on the oxygen of **1.9** can then trap the carbocation of **1.18** yielding the benzyl ether product **1.11** and byproduct **1.19**.



Scheme 1.5 S_N1 vs. S_N2 Mechanism of Bn-OPT Reactions

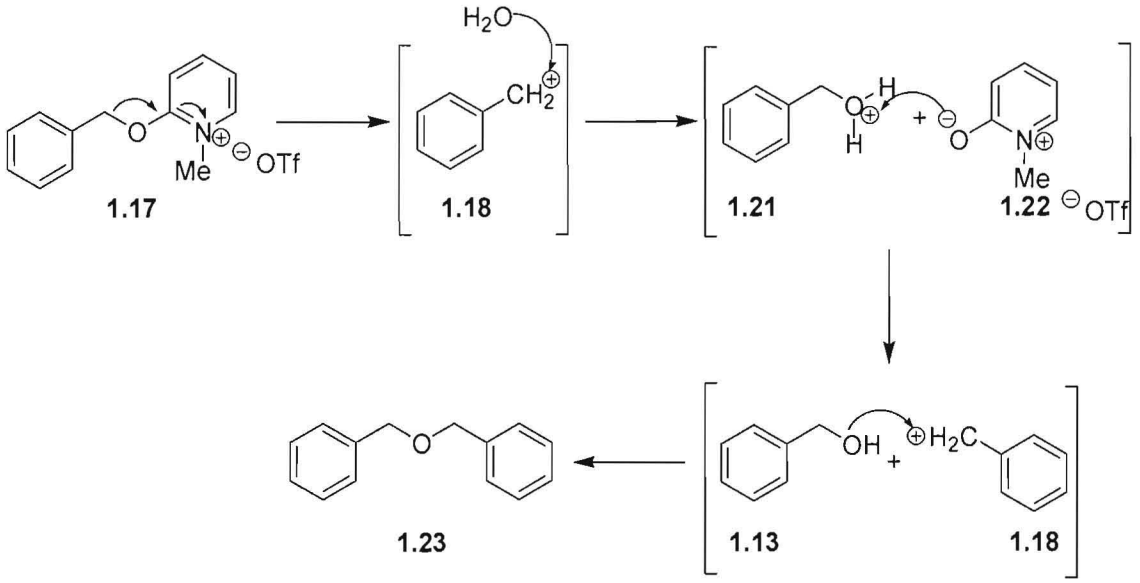
There is evidence to support an S_N1-like mechanism of benzylation.[8] The methoxy derivative of **1.17** failed to react under similar conditions to those of Table 1.1. This supports an S_N1-like mechanism because a methyl carbocation is not stable but the methoxy salt should be one of the best substrates to participate in an S_N2-like pathway. This is because there is no steric hindrance to backside attack and **1.19** is a very good leaving group. Second, the byproducts of early reactions run in toluene support an S_N1-like mechanism. The byproducts were ***o*-1.20** and ***p*-1.20** (Scheme 1.6) which indicated a Friedel-Crafts reaction with a highly nucleophilic benzylating agent like **1.18**.



Scheme 1.6 Byproducts of Bn-OPT Reactions in Toluene

The byproducts of the benzylation reactions with Bn-OPT also support an S_N1-like mechanism. The byproducts include pyridine **1.19** but also dibenzyl ether **1.23** seen in Scheme

1.7. This could be due to residual water trapping **1.18** leading to **1.13** instead of **1.11**. **1.13** can then trap another molecule of **1.18** to give **1.23**.



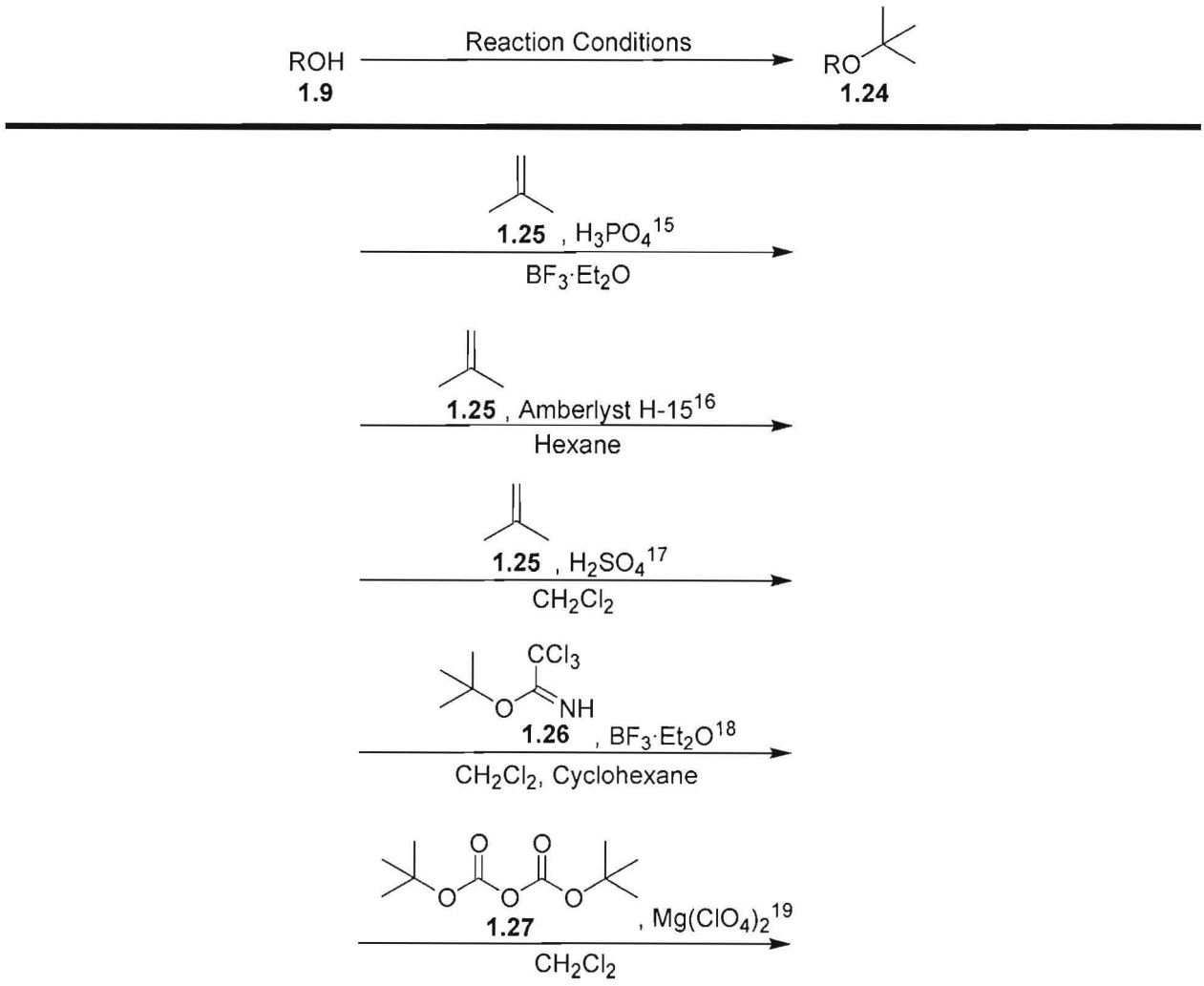
Scheme 1.7 Possible Mechanism for the Formation of Dibenzyl Ether

The final supporting evidence suggesting an S_N1-like pathway was the instability of the para-methoxybenzyl (PMB) derivative of Bn-OPT.[14] This PMB salt was insoluble in trifluorotoluene so a lepidine salt was synthesized to transfer the PMB group in $PhCF_3$ instead. $PhCF_3$ was used because the fluorine atoms deactivate the benzene ring by pulling electron density away from it. This helps get rid of the Friedel-Crafts byproducts ***o*-1.20** and ***p*-1.20**. The lepidine PMB salt was unstable at room temperature indicating that the resulting PMB carbocation was so stable that the salt readily decomposed to form it at 23 °C.

If the benzylation does in fact proceed via an S_N1-like mechanism then any substrate which can yield a stable carbocation should transfer that group to an oxygen nucleophile, namely that of an alcohol (**1.9**). This research focuses on one of the simpler stable carbocations, a *tert*-

butyl carbocation. If this analogue to Bn-OPT can be synthesized then it should transfer the *t*-butyl group to alcohols the way Bn-OPT transfers a benzyl group.

The *t*-butyl group is a very useful protecting group. It can protect a wide range of alcohols and is stable to many reagents excluding acids. Also, since there is a variety of easy ways to cleave this group the yields of step three of using a protecting group are typically very high. Despite this, there are not many ways to make *t*-butyl ethers (Scheme 1.8).[1]



Scheme 1.8 Current Methods for *t*-Butyl Installation on an Alcohol

All of the reactions in Scheme 1.8 involve harsh conditions. These conditions include using a protic acid like H_2SO_4,[17] a Lewis acid (BF_3),[18] or a strong oxidizing agent ($Mg(ClO_4)_2$)[19].

This can alter functional groups sensitive to acid or oxidation. Also, three of the strategies use **1.25**, isobutylene.[15-17] This makes the reaction very tedious since isobutylene boils at -6.9 °C and is a gas at room temperature. One reaction bubbles gaseous isobutylene directly into the reaction.[16] This means that the amount of gas used is not easy to measure and may require complex tubing or balloons. The other two strategies use liquid isobutylene,[15,17] which requires cold temperatures to condense the gas. The liquid must then be measured quickly and handled carefully so that the liquid isobutylene does not boil.

If protecting an alcohol with a *t*-butyl group can instead be as easy as mixing and heating like with Bn-OPT then this would greatly simplify synthesizing *t*-butyl ethers. Since **1.26** can serve as a source for a *t*-butyl fragment, a similar preactivated variant should transfer a *t*-butyl group as well. This research will attempt to synthesize this *t*-butyl transfer salt to be used under neutral conditions.

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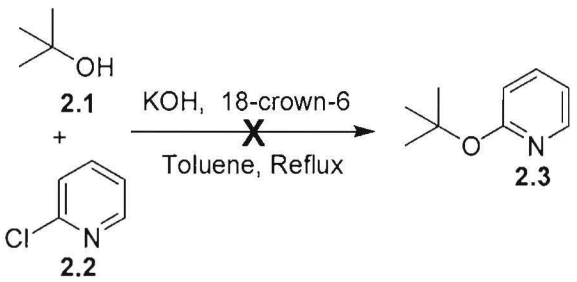
Synthesis and Application of 2-*tert*-Butoxy-1-methylpyridinium Triflate

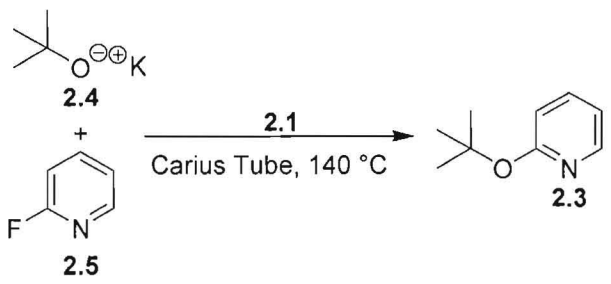
This project was an extension of the application of pyridinium salts in protecting oxygen and other nucleophiles. The goal was to synthesize and utilize a *t*-butyl protecting reagent. 2-*tert*-butoxy-1-methylpyridium triflate or *t*-BuOPT (**2.7**) should behave just like Bn-OPT (**2.10**) in transferring a *t*-butyl group via an S_N1-like mechanism.

It was initially thought that making *t*-BuOPT could be carried out in a similar fashion to the synthesis of Bn-OPT. The synthesis of Bn-OPT starts by refluxing benzyl alcohol (**2.11a** on Table 2.2, p. 22) and **2.2** in the presence of KOH and 18-crown-6 in toluene to give 2-benzyloxypyridine.[1] The same reaction, Scheme 2.1, was tried with **2.1** instead of benzyl alcohol.



Scheme 2.1 Proposed Synthesis of 2-*t*-Butoxypyridine

This reaction, carried out by Christian Hubley, did not yield **2.3**.[2] This is likely due to the fact that the bulky *t*-butoxide produced from **2.1** is a poor nucleophile. Other options to making **2.3** had to be explored. One reported successful synthesis of **2.3** shown in Scheme 2.2 was attempted. This strategy uses the more reactive **2.4** and **2.5** and high pressure in a Carius tube. It was ineffective, yielding only 2-5% of product.[2] Also, this reaction involves an expensive reagent, **2.5**, and there is a risk of explosions when using high pressure. For these reasons this strategy was abandoned and focus was shifted to modifying Scheme 2.1 instead.



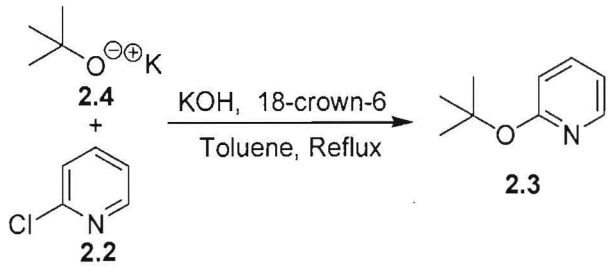
Scheme 2.2 Synthesis of 2-*t*-Butoxypyridine[3]

It was thought that if the more nucleophilic **2.4** was used in place of **2.1** in Scheme 2.1 that the desired reaction would occur. The 18-crown-6 would hopefully trap the potassium counter ion leaving a more reactive "naked" *t*-butoxide anion. The first attempt at this modified strategy, entry 1 of Table 2.1, yielded a black solution that once isolated and purified actually yielded 25% of product **2.3**.[2] The temperature, length of reaction and equivalents of potassium t-butoxide, **2.4**, all required optimization. Early trials focused on this optimization[2] and many unsuccessful attempts were made to reproduce the optimized results in Table 2.1. A mixture of Scheme 2.1 and Scheme 2.2 was even attempted utilizing the modified Scheme 2.1 but also the high pressure of Scheme 2.2 and no 18-crown-6. This high pressure strategy did not yield any product and was once again abandoned.

During the purification of entry 6 in Table 2.1 it was discovered that impure solvents were being used which destroyed the crude recovery. Eventually, the recoveries from entries 7 through 10 were combined and distilled to yield 194 mgs. This along with previously prepared **2.3** was used for later reactions.

After **2.3** was first synthesized, the nitrogen was methylated[2] with MeOTf (**2.6**) in the same fashion as Bn-OPT.[1] At first, this reaction failed as ^{1}H NMR spectra showed decomposition of the newly formed salt and loss of the *t*-butyl group.[2] Later attempts of methylation with MeOTf worked yielding *t*-BuOPT (**2.7**) but the salt appeared to melt rapidly

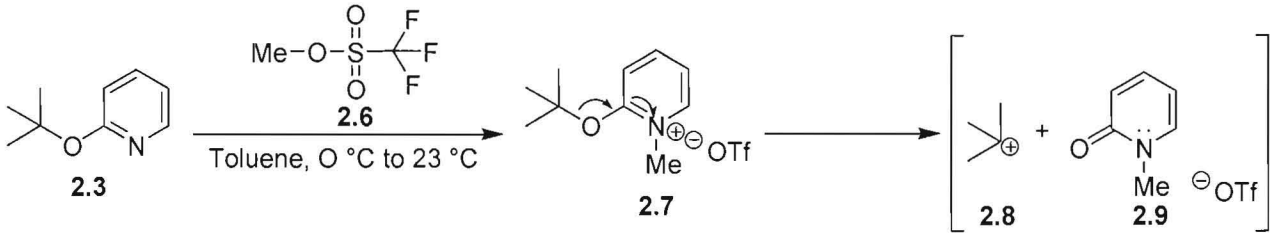
during purification. ^{1}H NMR again showed that the salt was decomposing. Possible decomposition products are shown in Scheme 2.3. It was found that the salt was only stable if stored in the freezer.[2]



Entry	Temperature	Time	Potassium *t*-butoxide equiv.	Product Yield (%)
1[a]	23 °C to reflux	20 min	3	25
2[a]	0 °C to 23 °C	24 h	3	13
3[a]	0 °C to reflux	24 h	3	89
4[a]	0 °C to reflux	24 h	2	87
5[a]	0 °C to reflux	24 h	1.1	63
6[b]	0 °C to reflux	24 h	2.6	76*
7[b]	0 °C to reflux	24 h	2.6	25*
8[b]	0 °C to reflux	24 h	2.6	35*
9[b]	0 °C to reflux	24 h	2.6	38*
10[b]	0 °C to reflux	24 h	2.6	29*

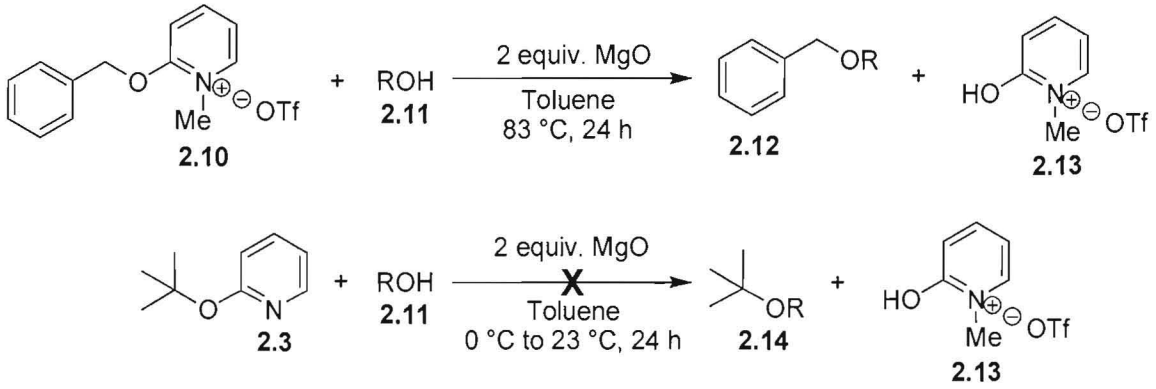
a. Christian Hubley Data[2]
b. Reproduced Results
* Crude recovery

Table 2.1 Optimization of 2-*t*-Butoxypyridine Formation



Scheme 2.3 Possible Mechanism for the Generation of a *t*-Butyl Carbocation

Since the unstable *t*-BuOPT had to be kept in the freezer, etherification of alcohol reactions presented some difficulties. The salt had to be removed from the freezer and warmed up enough so that it could be weighed out, but not overheated or else it would begin to decompose. Early attempts at generating *t*-butyl ethers were carried out in the same way that benzyl ether **2.12** is made from Bn-OPT, **2.10**, with the exception of the reaction temperature. Since *t*-BuOPT readily decomposes at 23 °C it was thought that no heat would be necessary for the *t*-butyl transfer to occur. However, as Scheme 2.4 shows, this reaction failed.

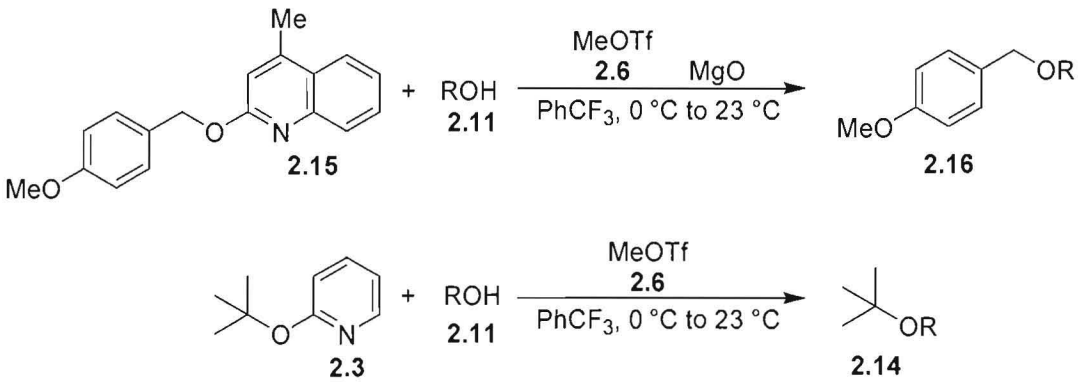


Scheme 2.4 Failed Synthesis of *t*-Butyl Ethers[2]

This strategy was attempted again with heating to 83 °C and this led to **2.14**. Since this reaction should not require heat the reaction was observed further. It was noted that upon adding MgO to the reaction mixture *t*-BuOPT precipitated out of solution and required heat to

redissolve. Later reactions were attempted without MgO from 0 °C to 23 °C which resulted in the successful synthesis of **2.14**.[2]

This research focused on generating *t*-BuOPT (**2.7**) *in situ*. This was pursued because the *para*-methoxybenzyl (PMB) variant[4] of Bn-OPT has similar properties to *t*-BuOPT. Once **2.15** was methylated by MeOTf, the PMB salt was unstable at 23 °C and decomposed. However, when **2.15** was mixed with **2.11** in the presence of MeOTf, **2.16** was formed in comparable high yields to the Bn-OPT reactions. It is believed that once methylated, the PMB salt decomposed to yield a PMB carbocation similar to **2.8** that was then trapped by **2.11** to yield **2.16**. As Scheme 2.5 shows, the analogous reaction with **2.3** was carried out with the same reaction conditions as previous successful trials with salt **2.7**.



Scheme 2.5 *In Situ* Generation of Transfer Salts Leading to Ethers

The reactions done generating the salt *in situ* did not behave as expected. Initially, the reaction with alcohol **2.11f** of Table 2.2 (p.22) was run at 23 °C since the salt decomposes at this temperature. This reaction did not yield product but an insoluble salt was left behind. In the next trial with **2.11f**, the reaction mixture was heated to 50 °C to dissolve the formed salt and help the decomposition of the salt to form the *t*-butyl carbocation **2.8**. This failed to produce product as well. The reaction was then attempted with **2.11a** and the reaction mixture was again

heated to 50 °C. Since this failed to yield any product it was thought that perhaps heating was causing isobutylene to form and bubble away. This led to the next reaction with **2.11a** to be run in an ice/water bath to try to suppress isobutylene formation. ^{1}H NMR of the crude recovery showed a shifting of the benzyl protons upfield to 4.46 and incorporation of the *t*-butyl group at 1.29 as expected.[5] This product was very difficult to separate from the impurities both via TLC and flash column chromotography. Impure product was obtained in such an insignificant yield that no further purification was attempted.

Alcohols were then screened to see which ones were the easiest to visualize via TLC both by UV fluorescence and stains. Alcohols **2.11g** and **2.11h** were chosen and reactions were run in ice/water baths again. ^{1}H NMR of crude recoveries indicated that some reaction occurred with both alcohols although it is unclear exactly what happened. Entry 8 of Table 2.2 (p. 22) with alcohol **2.11g** (PMB) is a prime example of this. As Figure 2.1 shows, the protons on the aromatic ring in the crude recovery have shifted upfield compared to the starting material while still showing the same splitting pattern and integration as the analogous PMB protons. Also, the benzyl protons are absent and the methoxy protons are unaffected in the crude recovery. This indicates that some reaction may be occurring on or near the alcohol shifting the aromatic protons and affecting the benzyl protons. Although some reaction is occurring, the end result is evidently not *t*-butyl transfer since no *t*-butyl protons are seen in the spectra. It is possible that the *t*-butyl ether is being made but is rapidly decomposing. This decomposition could be occurring in the reaction flask or during the work up. The reaction conditions and work up require optimization that will hopefully alleviate these issues.

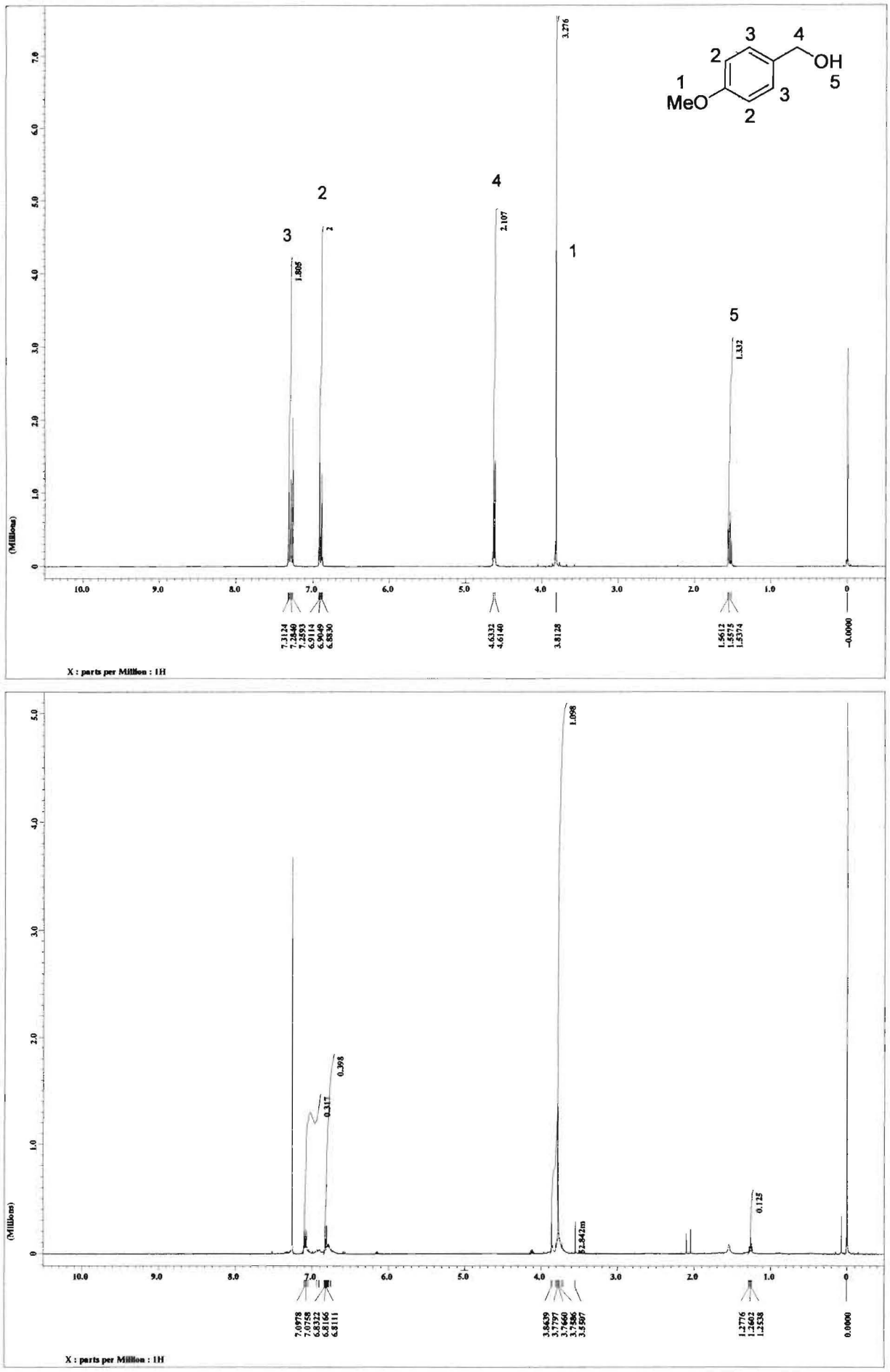
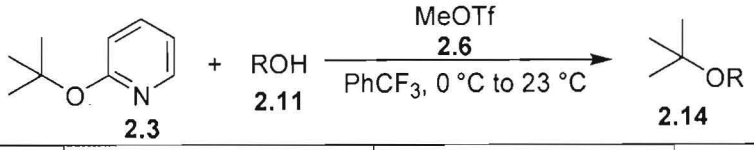
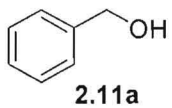
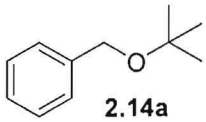
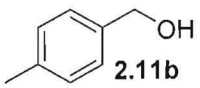
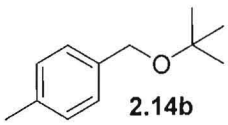
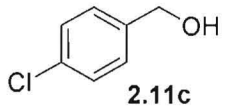
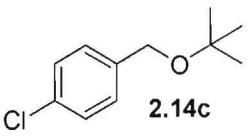
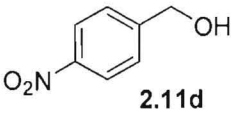
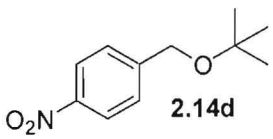
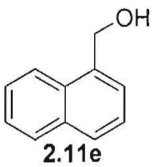
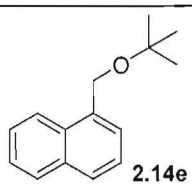
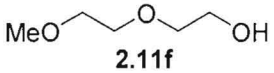
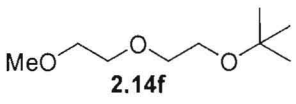
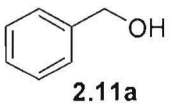
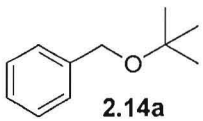
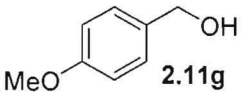
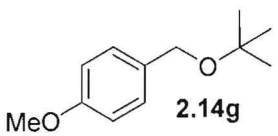
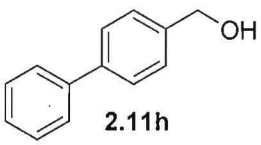
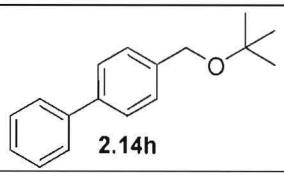


Figure 2.1 ^{1}H NMR of Starting Material (top) vs. Unknown Crude Recovery (bottom)

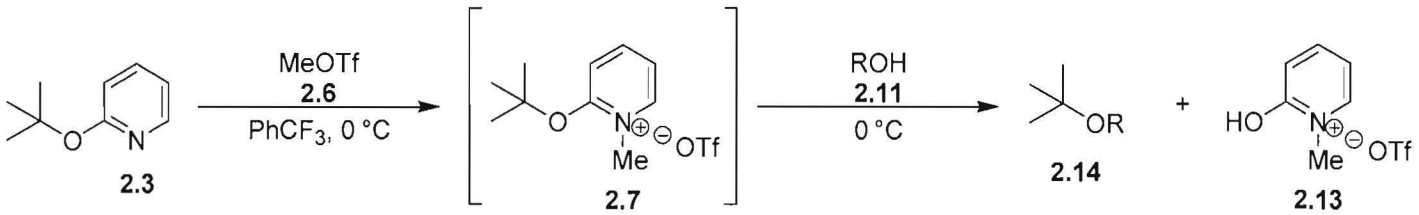


Entry	Alcohol (2.11)	*t*-Butyl Ether (2.14)	Yield (%)
1[a]	 2.11a	 2.14a	83
2[a]	 2.11b	 2.14b	81
3[a]	 2.11c	 2.14c	78
4[a]	 2.11d	 2.14d	42
5[a]	 2.11e	 2.14e	61
6[b]	 2.11f	 2.14f	–
7[b]	 2.11a	 2.14a	n.d.
8[b]	 2.11g	 2.14g	–
9[b]	 2.11h	 2.14h	–

a. Utilized Preformed Transfer Salt[2]
b. *In Situ* Generation of Transfer Salt

Table 2.2 Results of *t*-Butyl Transfer

The next step in this reaction is to optimize the *in situ* generation of the *t*-butyl transfer salt and subsequent ether formation with an alcohol. It is hoped that this will be achieved by first generating the salt *in situ* at 0 °C or colder. Once a sufficient amount of salt has been formed the alcohol (**2.11**) will be dripped in slowly (Scheme 2.6). It is our belief that this method will lead to the formation of a *t*-butyl ether (**2.14**).



Scheme 2.6 Proposed Synthesis of *t*-Butyl Ethers

After optimization of the *in situ* transfer of the *t*-butyl group, it is hoped that this process can be expanded to a variety of nucleophiles. First attempts will be made with carboxylic acids to make esters as was done with Bn-OPT. Eventually we hope to expand carbocation chemistry, which is a very reactive intermediate. Carbocation chemistry is not often utilized because harsh conditions are required to generate a carbocation. It is our hope that preactivated *t*-BuOPT will generate a very electrophilic *t*-butyl carbocation which can react with weak nucleophiles. It will then be possible to form a variety of new bonds with many different nucleophiles.

References

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2. Hubley, C. T. N. H. Synthesis and Mechanistic Study of Alkoxypyridinium Salt Derivatives. Master's Thesis. Ball State University, Muncie, IN, July 2011.
3. Al-Awadi, N; Ballam, J.; Hemblade, P. R.; Taylor, R. The Mechanisms of Thermal Eliminations. Part 11. Rate Data for Pyrolysis of 2-Alkoxypyridines to 2-Pyridone, and of 2-Ethoxypicolines to 2-Picolones: Nature and Polarity of the Transition State *J. Chem. Soc., Perkin Trans. 2* **1982**, 1175-1178.
4. Nwoye, E. O.; Dudley, G. B. Synthesis of *para*-Methoxybenzyl (PMB) Ethers under Neutral Conditions. *Chem. Commun.* **2007**, 1436-1437.
5. Barbasiewicz, M.; Mąkosza, M. Intermolecular Reactions of Chlorohydrine Anions: Acetalization of Carbonyl Compounds under Basic Conditions. *Org. Lett.* **2006**, *8*, 3745–3748.

Experimental Procedures

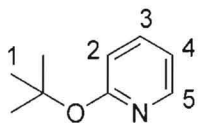
Reagents: All reagents were used directly from the manufacturer without further purification.

Solvents: Toluene was dried by a Vacuum Atmosphere (VAC) solvent purification system and stored over 4 Å molecular sieves. All other solvents were used directly from the manufacturer.

General Reaction Procedures: Glassware, NMR tubes, stir bars, needles, syringes, and reflux condensers were dried overnight in a 150 °C oven and cooled to room temperature in a Bel-Art Scienceware dessicator. Glassware was evacuated on a high vacuum via an oil pump. Glassware was then pumped with argon (Ar) and reactions were performed under argon as well. An IKA hot plate/stirring mantle with a digital thermometer was used to heat and stir reactions as well as to read temperatures of oil baths or ice/water baths. Vacuum filtration was performed with a KNF Laboratories oil-free filtration pump and a Büchner funnel. Solvents were evaporated by a Büchi Rotavapor RII with a Büchi oil-free vacuum pump (~ 7.5 mmHg).

Purification: Thin Layer Chromatography (TLC) was performed on Whatman UV 254 aluminum backed silica gel plates. Plates were viewed via a UVP compact UV lamp at 254 nm and/or stained primarily with *p*-anisaldehyde solution. Occasionally, iodine, 2-4-dinitrophenylhydrazine (DNP) solution, or vanillin solution was used. Flash column chromatography was performed with Dynamic Adsorbents Inc. Flash Grade Silica Gel (32-63 Å porosity).

Analytical Data: Proton Nuclear Magnetic Resonance (^{1}H NMR) spectra were recorded on JEOL (300 MHz) or (400 MHz) instruments. $CDCl_3$ with 0.05% v/v TMS (Cambridge Isotope Laboratories Inc.) was used for the solvent. ^{1}H NMR shifts are reported in parts per million (ppm) and are referenced to the TMS peak in the $CDCl_3$ solvent.



2.3

2-*tert*-butoxypyridine. A 25-mL, two-necked, round bottom flask equipped with a magnetic stir bar, a rubber septum and a reflux condenser was charged with potassium *t*-butoxide (1.6199 g, 13.71 mmol, 2.6 equiv.), anhydrous toluene (12.5 mL) and 18-crown-6 (96.2 mg, 0.360 mmol, 0.066 equiv.). The reaction mixture was then placed in an ice/water bath and stirred for 10 min. The flask was then charged with 2-chloropyridine (0.5 ml, 5.27 mmol, 1.0 equiv.) dropwise through the rubber septum over a period of 10 min. The rubber septum was replaced with a glass stopper and the flask was placed in an oil bath. The oil was heated to approximately 143 °C at which point the reaction mixture began to reflux. The reaction was refluxed for 24 hours while stirring. The reaction was then removed from the heating/stirring mantle and allowed to cool to room temperature. The stopper and condenser were removed and water was slowly dripped into the reaction to quench any leftover *t*-butoxide until the bubbling stopped. The reaction mixture was then diluted to 30 mL with c.a. 23 ml of ethyl acetate and transferred to a 125 ml separatory funnel. The organic layer was washed three times

with 20 ml of water. The aqueous layer was then back extracted with 10 ml of ethyl acetate three times. The two organic layers were combined and dried over sodium sulfate. The sodium sulfate was separated via vacuum filtration and the organic layer was concentrated in vacuo on a rotary evaporator. 10 ml of methanol was then added to azeotrope any leftover toluene and concentrated on the rotary evaporator again. The crude products from 5 trials were combined and distilled via a Büchi Glass Oven Kugelrohr reading 141 °C at ≈ 5 mmHg (combined 5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, J = 1.8, 4.8, $1H_5$), 7.50 (ddd, J = 2.2, 7.3, 8.4, $1H_3$), 6.80 (dd, J = 5.0, 6.2, $1H_4$), 6.64 (d, J = 8.4, $1H_2$), 1.58 (s, $9H_1$).

(Millions)
X : parts per Million : 1H
0.0000
1.5789
8.1226
8.1153
8.1098
7.5053
7.5026
7.4971
6.7974
6.7946
6.6518
6.6307
0.808
0.809
0.845
0.722
1
2
3
4
5
6
N
O